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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,979	03/22/2001	Gary de Jong	24601-416	7635

24961 7590 03/25/2003

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EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 03/25/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/815,979

Applicant(s)

DE JONG ET AL.

Examiner

Daniel M Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-83 and 140-143 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-83 and 140-143 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8,10,11,15
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

This is the First Office Action on the Merits of the application filed 22 March 2001.

Receipt and entry of the preliminary amendments filed 25 May 2001 (Paper No. 4) and 8 January 2003 (Paper No. 14) is acknowledged. Claims 6, 8, 14, 36, 39, 42, 51, 53, 59, 67, 71, 79, 87, 89, 94, 96, 102, 104, 110, 112, 118, 120, 127, 133, 138, 140, 141 and 143 were amended in Paper No. 4 and claims 84-139 were canceled in Paper No. 14. Claims 1-83 and 140-143 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-83 and 140-143 in Paper No. 14 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26, 28-33, 38, 39, 41-48, 53-57, 65, 69, 71-76, 140 and 141 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

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in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims are directed to methods of introducing nucleic acids into cells comprising the use of a delivery agent and kits comprising said delivery agent. The specification defines delivery agents as, "compositions, conditions and physical treatments that enhance contact of nucleic acid molecules, such as DNA, with cells and/or increase the permeability of cells to nucleic acid molecules such as DNA" (page 19). Thus the claims encompass methods of using, and kits comprising a broad and disparate genus of any and all compositions, conditions and physical treatments having the functional characteristics set forth. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 3, page 71434). As the claims are limited to comprising the delivery agent, the delivery agent is a critical element of the claimed subject matter and thus must be adequately described.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). The specification, beginning on page 19 and continued through page 23, describes a variety of cationic compounds and two forms of energy having the features of a delivery agent.

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However, given the enormous breadth of the genus (comprising all compounds, conditions and physical treatments that enhance delivery of a nucleic acid into a cell) and the fact that the examples provided are limited only to cationic compounds and two forms of energy, the species provided clearly are not representative of the full genus. With regard to the relevant identifying characteristics, the specification does not limit the genus to a compound of a given structure, to any given form of energy or to any type of physical treatment. Therefore, the only disclosed identifying characteristic, common to all of the species comprised within the genus, is that they function as a delivery agent. However, it is not sufficient to define a delivery agent solely by its principal biological property, i.e. it enhances contact of nucleic acid molecules with cells and/or increase the permeability of cells to nucleic acid molecules, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any agent with that biological property. Also, naming a type of material or physical treatment generically thought to exist, in the absence of knowledge as to what that material or treatment consists of, is not a description of that material or physical treatment. Thus, claiming methods of using or compositions comprising all materials or treatments that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for

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the broad class of delivery agents. Therefore, only the described delivery agents set forth in the specification meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 31 and 33 are additionally rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for "a cell capable of the generation of a specific organ". The cell of the claims encompasses a genus any and all cells capable of generating any organ. Cells capable of generation of a specific organ are not conventional in the art, and the disclosure does not provide a single example of a cell encompassed by the genus. The description of a cell capable of the generation of a specific organ is limited a recitation of function without any details as to what such a cell would look like. For reasons set forth above, simply stating that a cell capable of the generation of a specific organ will be used in the method does not adequately demonstrate possession of the cell.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for introducing a nucleic acid into a cell *in vitro*, does not reasonably provide enablement for *ex vivo* or *in vivo* gene transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

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and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and breadth of the claims: The claims are directed to a method for introducing a nucleic acid molecule into a cell, wherein the nucleic acid is delivered *in vitro*, *ex vivo* or *in vivo*. The specification teaches that *ex vivo* or *in vivo* gene transfer can be used to deliver a nucleic acid molecule into an individual for the purpose of therapy (see especially beginning the page 24, line 30 and continued through page 28, line 9). As the specification provides no other practical utility for *ex vivo* or *in vivo* gene transfer, the claims clearly encompass methods of *ex vivo* or *in vivo* gene therapy. The enabling disclosure must therefore teach the skilled artisan how to use the claimed method for the purpose of gene therapy.

State of the prior art and level of predictability in the art: At the time of filing, *ex vivo* or *in vivo* gene therapy, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for

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more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

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Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published shortly after filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claims of the instant application are not limited to treatment of any particular

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condition and thus encompass methods of treating any and all conditions that might be amenable to gene therapy. However, Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings

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demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanuelli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of direction provided by the inventor existence of working examples: The teachings of the specification provide only that the described compositions can effectively

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transfer DNA into cells *in vitro* (see especially Examples 4-7). The disclosure does not demonstrate that the compositions work as vehicles *in vivo*, does not address any of the core issues related to the unpredictability of gene therapy described herein above and provides no reason to believe that the disclosed methods will enable the skilled artisan to successfully treat a patient.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods of the instant claims without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The claim is indefinite in its recitation of "the cationic compound". There is no antecedent basis for "the cationic compound" in claim 48. In the interest of compact prosecution, the claim has been examined with the assumption that it should depend from claim 49.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: The following rejections apply to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claims. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 1, 7, 9, 10, 12-14, 30-32, 58 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Strauss *et al.* (1992) *EMBO J.* 11:417-422.

Strauss *et al.* teaches a method for introducing a nucleic acid molecule into a cell comprising: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to the delivery agent; and (c) contacting the cell with the nucleic acid molecule wherein step (a) is

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performed first and steps (b) and (c) are performed simultaneously (see especially the third full paragraph on page 422). Thus, the teachings of Strauss *et al.* anticipate the limitations of claim 1.

Strauss *et al.* further teach the method of claim 1 wherein: the nucleic acid molecule is an artificial chromosome according to claim 7; the nucleic acid molecule is exposed to the delivery agent *in vitro* according to claim 9; the contacting of the nucleic acid with the cell is effected *in vitro* according to claim 10; the delivery agent comprises DOTMA according to claims 12-14; and the cell is a primary animal cell according to claims 30-32.

The method described above also anticipates the limitations of claim 58, which is directed to a method comprising: (a) contacting the nucleic acid with a composition comprising a cationic lipid; and (b) contacting the nucleic acid molecule with a cell, and the limitations of claims 61-64 which depend from claim 58 and are directed to the method wherein the nucleic acid molecule is an artificial chromosome (claim 61), the cell is an animal cell (claim 62), the cell is a primary cell (claim 63) and the nucleic acid molecule is contacted with the cell *in vitro* (claim 64).

The method taught by Strauss *et al.* is the same as the instant claimed method; therefore the limitations of the claims are anticipated by Strauss *et al.*

Claims 1, 2, 9-17, 19, 26-28, 30-32, 58, 61-64, 140, 142 and 143 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (1997) *Invest. Radiol.* 32:723-727 (made of record in the IDS filed 7 September 2001).

Unger *et al.* teaches a method for introducing a nucleic acid molecule into a cell comprising: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to a

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delivery agent; and (c) contacting the cell with the nucleic acid molecule wherein, in step (a) the nucleic acid is exposed to a cationic compound and in step (b) the cells are exposed to ultrasound (see especially the first and second full paragraphs on page 725 and Figure 4 and the caption thereto). Thus, the method of Unger *et al.* anticipates the limitations of claims 1, 2, 11 and 26-28.

Unger *et al.* further teach the method of claim 1 wherein: the nucleic acid molecule is exposed to the delivery agent *in vitro* according to claim 9; the contacting of the nucleic acid with the cell is effected *in vitro* according to claim 10; the delivery agent comprises DPEPC, DOPE and/or DMRIE-C according to claims 12-14; and the cell is a immortalized animal cell according to claims 30-32. As indicated above, the method of Unger *et al.* comprises a delivery agent that is ultrasound, which anticipates the limitations of claims 15-17, applied as a continuous pulse according to the limitations of claim 19 (see especially the paragraph bridging pages 723 and 724).

The method described above also anticipates the limitations of claim 58, which is directed to a method comprising: (a) contacting the nucleic acid with a composition comprising a cationic lipid; and (b) contacting the nucleic acid molecule with a cell, and the limitations of claims 61-64 which depend from claim 58 and are directed to the method wherein the nucleic acid molecule is naked DNA (claim 61), the cell is an animal cell (claim 62), the cell is an immortalized cell (claim 63) and the nucleic acid molecule is contacted with the cell *in vitro* (claim 64).

Finally, Unger *et al.* teaches all of the components comprised within the kit of claims 140, 142 and 143; therefore, the teachings of Unger *et al.* anticipate the claimed kit.

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Claims 1, 9, 10, 12-14, 30-32, 58, 61-66, 70 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by McDonald *et al.* (1998) U.S. Patent No. 5,837,283.

McDonald *et al.* teaches a method for introducing a nucleic acid molecule into a cell comprising: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to the delivery agent; and (c) contacting the cell with the nucleic acid molecule wherein step (a) is performed first and steps (b) and (c) are performed simultaneously (see especially Example 1, beginning column 24). Thus, the teachings of anticipate the limitations of claim 1.

McDonald *et al.* further teach the method of claim 1 wherein: the nucleic acid molecule is exposed to the delivery agent *in vitro* according to claim 9; the contacting of the nucleic acid with the cell is effected *in vivo* according to claim 10; the delivery agent comprises DDAB or DOTAP and DOPE according to claims 12-14; and the cell is a primary animal cell according to claims 30-32.

The method described above also anticipates the limitations of claim 58, which is directed to a method comprising: (a) contacting the nucleic acid with a composition comprising a cationic lipid; and (b) contacting the nucleic acid molecule with a cell, and the limitations of claims 61-64 which depend from claim 58 and are directed to the method wherein the nucleic acid molecule is naked DNA (claim 61), the cell is an animal cell (claim 62), the cell is an primary cell (claim 63) and the nucleic acid molecule is contacted with the cell *in vitro* (claim 64). In addition, McDonald *et al.* teaches mixing the nucleic acid with a delivery agent and administering the agent to a subject according to claims 65, 66, 70 and 72.

The method taught by McDonald *et al.* is the same as the instant claimed method; therefore the limitations of the claims are anticipated by McDonald *et al.*

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Claims 1, 3-10, 12-14, 30-33, 58 and 60-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Hadlaczký *et al.* (February 2000) U.S. Patent No. 6,025,155.

Hadlaczký *et al.* teaches that the artificial chromosomes disclosed therein, having a size of 20-30 Mb (Figure 2), can be introduced into cells using lipid mediated transfer (paragraph bridging columns 5 and 6) which one of ordinary skill in the art would understand to comprise: (a) exposing the nucleic acid molecule to a delivery agent; (b) exposing the cell to the delivery agent; and (c) contacting the cell with the nucleic acid molecule wherein step (a) is performed first and steps (b) and (c) are performed simultaneously (see especially Example 1, beginning column 24). Thus, the teachings of Hadlaczký *et al.* anticipate the limitations of claims 1 and 3-8.

Hadlaczký *et al.* further teach the method of claim 1 wherein: the nucleic acid molecule is exposed to the delivery agent *in vitro* according to claim 9; the contacting of the nucleic acid with the cell is effected *in vitro* or *in vivo* (see especially the second full paragraph in column 19) according to claim 10; the delivery agent comprises various lipid-mediated carrier systems (third paragraph in column 20) according to claims 12-14; and the cell can be a plant or animal cell, a stem cell or an embryonic stem cell (paragraph bridging columns 5 and 6) according to claims 30-33.

The method described above also anticipates the limitations of claim 58, which is directed to a method comprising: (a) contacting the nucleic acid with a composition comprising a cationic lipid; and (b) contacting the nucleic acid molecule with a cell, and the limitations of claims 61-64 which depend from claim 58 and are directed to the method wherein the nucleic

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acid molecule is an artificial chromosome (claim 61), the cell is an animal or plant cell (claim 62), the cell is a embryonic cell (claim 63) and the nucleic acid molecule is contacted with the cell *in vitro* or *in vivo* (claim 64).

The method taught by Hadlaczký *et al.* is the same as the instant claimed method; therefore the limitations of the claims are anticipated by Hadlaczký *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 21, 2003


ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER